INTRODUCTION

Auditory neuropathy (AN) is a condition caused by a deficiency of synchronous neural activity of the cochlear nerve and is related to injuries that can affect the inner hair cell synapse, spiral ganglion, axon, the myelin sheath, and nerve dendrite [1-3].

The term has been used to describe a singular situation that affects both adults and children with diagnostic criteria that characterizes the normal functioning of outer hair cells, by examination of these otoacoustic emissions and the abnormal or absent operation of the cochlear nerve, through the presence of cochlear microphonic (CM) or by the absence or dyssynchrony of the waves generated in the auditory-evoked potential/brain response (ABR). Generally, patients still have difficulty in speech discrimination, inconsistent with the pure tone audiogram findings [1, 2].

The term AN was first used in 1996 and later changed to the AN spectrum disorder during the Conference of Consensus on Auditory Neuropathy/dyssynchrony in Como, Italy, in 2008 because of the different clinical forms of this peculiar disease [2, 4-6].

The pathophysiology of this condition remains unclear, although in recent years, the identification of genes involved in the pathogenesis of AN, both presynaptic and post-synaptic, has significantly contributed to the diagnosis and better understanding of the mechanisms involved in this clinical disorder [1, 6, 7].

In the past, AN patients were treated in different ways, depending on their degree of hearing loss. Thus, treatment ranged from a simple observance to the use of hearing aids and frequency modulation (FM) system with predominantly unsatisfying results, such as poor speech or hearing rehabilitation [8, 9].

As the conventional treatment of AN has proved, in most cases, refractory to conventional amplification, the cochlear implant (CI) approach is an alternative therapy for this condition [1, 3, 5].

OBJECTIVE: To describe the performance and results of CIs (cochlear implant) in patients with AN (auditory neuropathy) and to present a medical literature review.

MATERIALS and METHODS: Retrospective chart review of patients with AN who were treated with CI. The mesh terms used for the review in the Pubmed and Scopus databases were as follows: “hearing loss, cochlear implants, rehabilitation of persons with hearing impairment, auditory neuropathy”. Statistical Analyses: The Mann-Whitney test was performed.

RESULTS: The sample consisted of 10 patients. The mean age at surgery was 4.3 years, range 2-16 years. The average length of CI use was 5.2 years. The comparison of hearing levels before and after CI use showed a significant improvement in all patients, with p<0.05. All of them also reported an increase in overall satisfaction 1 year after the procedure. A CI is the standard treatment for the hearing rehabilitation of patients with severe profound hearing loss who do not benefit from conventional hearing aids. There are diseases such as AN that also invoke a discussion in the literature regarding CI benefits.

CONCLUSION: Individuals with AN demonstrated a significant gain in hearing levels and language use with CI.

KEYWORDS: Auditory neuropathy spectrum disorder, evoked auditory brainstem response, otoacoustic emissions, GJB2, hearing loss, cochlear implants
Cochlear implants (CI) currently has ample evidence for its efficacy in the treatment of various forms of deafness, from unilateral to bilateral cases with severe to profound hearing loss. It also has been shown as an alternative for hearing rehabilitation in many conditions, such as in deafness with residual hearing at low frequencies and AN. In AN cases, CI is an option when the patient has not had a good response to conventional hearing aids and an adequate development of speech [1, 3, 5, 10, 11].

Although it has been demonstrated that the earlier use of CI in children with AN with severe or profound hearing loss leads to an important benefit in most cases, the situation is still challenging in cases when the hearing loss is moderate [1, 3]. Thus, CI has shown conflicting results worldwide, probably because AN must be heterogeneous and have different etiologies [3].

A recent systematic review evaluated the improvement of speech development in children with AN treated with CIs and showed favorable results after CI regarding hearing and speech parameters but concluded that the evidence for CI is still weak and further studies are needed to clarify where and when CI could be applied as a good option for pediatric patients with AN [10].

Regarding the etiologic heterogeneity of AN, it is not surprising that the auditory performance of CI treatment in AN patients is also variable. Therefore, the use of CIs for individuals with AN has been relatively controversial in the literature [13, 14].

The identification of specific mutations involved with AN has implications not only for diagnosis but also for rehabilitation because a good outcome is expected with CI use when the disturbance is due to presynaptic mutations (OTOF gene) or postsynaptic mutations in the distal portions of the auditory fibers (DIAPH3 gene). However, it is expected that CIs will have limited benefit for all forms of AN involving the auditory nerve [14, 15]. Therefore, the genetic and molecular diagnosis of AN is also important in the choice of an appropriate treatment and follow-up of those subjects.

Cochlear implants (CI) is becoming a choice of treatment for patients with AN. This kink of the hearing disorder with mild-to-moderate hearing loss remains a challenge in terms of the treatment options, even to experts in this area.

Thus, this paper aims to study and demonstrate the performance and developing speech skills of pediatric patients with AN spectrum disorder treated with CI and to evaluate this device as a treatment option.

MATERIAL and METHODS
A cross-sectional and case series study was conducted, through a retrospective analysis of the records of patients diagnosed with bilateral hearing loss, suspected of AN spectrum disorder (NA), followed in the hearing center at a tertiary university hospital and undergoing CI surgery.

The parameters studied were age, sex, onset of hearing loss (congenital, childhood, adolescence, or adult), gestational/perinatal/genetic background, and the results of electrophysiological hearing tests, namely ABR, otoacoustic emissions by distortion product (OAE), and a search for CM.

Perinatal and gestational histories were any situations described in the past of the patients, such as prematurity, jaundice, kernicterus, neonatal intensive unit hospitalization, meningitis, severe neonatal infections (such as sepsis and pneumonia), genetic syndromes, concomitant neurological diseases, infectious diseases (such as rubella and toxoplasmosis), clinical systemic comorbidities (such as hypertension and diabetes mellitus), and a family history of deafness.

The age group was defined as the beginning of the onset of symptoms, as follows: congenital (up to 1 year old), childhood (between 1 and 10 years old), adolescents (between 11 and 18 years of age), or adult (over 18 years life). Adults were excluded from this paper.

The clinical diagnosis of AN was established as follows: ABR with missing or abnormal responses and the presence of OAE and/or of CM with no anatomical alteration of the VIII cranial nerve. All patients had no acoustic reflex, and the presence of the cochlear nerve was assessed by nuclear magnetic resonance (MRI) and computed tomography (CT).

Molecular Study
Genomic DNA was extracted from patients’ peripheral venous blood according to standard protocols. GJB2 mutations were screened by a direct sequencing of the gene coding region [16, 17] and the exon 1 and flanking splice donor site [18].

Genomic DNA was extracted from patients’ peripheral blood, according to standard protocols. All samples were tested for mutations in the GJB2 gene as well as for the deletions del(GJB6-D13S1830) and del(GJB6-D13S1854) in the GJB6 gene, the mitochondrial mutation m.A1555A>G in the MTRNR1 gene, and the p.Q829X mutation in the OTOF gene. Mutations in the GJB2 gene were screened by direct sequencing of the coding region of the gene [19, 20].

Multiplex-PCR methodology was used to detect the del (GJB6-D13S1830) and del(GJB6-D13S1854) mutations in the GJB6 gene [21, 22]. The investigation of the mutations m.1555A>G and p.Q829X was performed using PCR, followed by digestion with BsmAI (New England BioLabs, Inc.; Ipswich, MA, USA) and BfaI (New England BioLabs, Inc.) restriction endonucleases, respectively [23, 24].

Inclusion and Exclusion Criteria
Inclusion criteria were patients with AN submitted to CIs with bilateral sensorineural hearing loss, normal otoscopy, an absence of middle ear disease, and no acoustic reflex.

Clinical spectrum of AN was considered when audiological tests were compatible with the following:

A) OAE present and ABR absent, or 
B) OAE absent and ABR absent and CMs present, or 
C) imaging (MRI/CT) showing the presence of VIII cranial nerve and excluding retrocochlear alterations.

All patients who did not fulfill these criteria were excluded from the study.
Sample: Patients with a clinical diagnosis of AN accompanied in the auditory hearing health care service of a tertiary care university hospital in the last 3 years submitted to CIs.

Only patients who had undergone audiological and electrophysiological testing with our team of speech experts with the same equipment were included in the sample.

Adults were excluded from this study and only pediatric patients were studied.

Audiological Evaluation
Audiological tests were performed including impedanciometry, speech, and pure tone audiometry. The tests were performed using an audiometer AC30-SD25 (Interacoustics; Copenhagen, Denmark), calibrated according to ISO 389 standards/64.

The Otoacoustic Emissions (OAE) distortion products were performed at frequencies of 700-8,000 Hz with a stimulus at 65-55 dB SPL, with a frequency ratio of 1.22. OEA was considered present when the signal/noise ratio was greater than 6 dB, and with a reproducibility ≥70%.

The tests from ABR and CM were performed with insert earphones. A stimulus of 100 dB HL was used for ABR covered with frequencies between 250 and 8,000 Hz, with a duration of 100 microseconds, and condensed and rarefied polarities. The abnormality of ABR was defined as the absence of wave formation or severe changes in morphology of the same with up to a 100 dB HL stimulus.

Cochlear Microphonism (CM) was evaluated in tests from ABR, with the feature of inverting the polarity (condensed and rarefied). When CM was positive with a stimulus of 100 dB, the HL electrophysiological threshold, in decreasing order, was researched.

For ABR, which was repeated at least twice, the AT-235 device (Interacoustics; Copenhagen, Denmark), was used.

Hearing loss impairment was classified through audiometry stratification into mild, moderate, severe/severe, or profound hearing loss [20].

Speech perception tests: During preoperative evaluation, all subjects underwent a speech perception test on the same day of their surgery. The speech perception test was based on several studies in the English language, adapted and developed for Portuguese language by Bevilacqua et al. [24]. Patients performed the tests with hearing aids, in a quiet and peaceful place (best aided condition).

Postoperatively, all subjects repeated the speech perception test with at least 1 year experience with the CI. The tests were performed using CI. The same audiologist performed all the tests (pre- and postoperative).

Three protocols to evaluate the patients’ performance language and hearing were used because most of them were children and pre-lingual developed. The scales used were as follows: IT MAIS (Meaningful Auditory Integration Scale for Young Children), MUSS (questionnaire for assessing oral language), and GASP (The Glendonald Auditory Screening Procedure, review of speech perception in profound deaf children from five years old) [27-29].

Such scales are widely used in this age group of patients and were adapted to the Portuguese language. IT MAIS and MUSS are protocols that are answered by the parents, but these scores are determined by the inquiring professional based on the examples that parents give for each question. It is a way of assessing patients in the first year of implant because they are still in the receptive language stage and have no spoken language, highlighting that IT MAIS has a greater focus on hearing, whereas the MUSS score has a greater focus on language acquisition [27-29]. The GASP has been used in patients aged more than 5 years.

Subjective evaluations: When patients did their postoperative speech tests, they were asked to rate the quality of their experience with CI compared to last year on a Likert scale ranging from 0 to 10, similar to the visual analog scale. A score of 0 indicates that the user regretted the intervention and would not recommend it to others and felt that they were better off before with just their hearing aids. A score of 10 indicates that the user was completely satisfied with the work and highly recommended it.

Statistical Analysis
The data were analyzed using descriptive analysis, with the mean, median, and standard deviation tabs. The software SIGMA XL was used to perform all statistical analysis (SigmaXL Inc.; Kitchener, Ontario, Canada).

The Chi-square and the Mann-Whitney test were used to compare the groups of samples as they are nonparametric tests applied for two independent samples.

The confidence interval was of 95%, and a p value of <0.05 was considered statistically significant.

Ethical Considerations
This study was previously approved by the Research Ethics Committee of the Faculty of Medical Sciences of the University of Campinas (Report number 396/2006).

RESULTS
A total of 19 patients were selected, but only 10 patients completed the full inclusion criteria presented above. Table 1 summarizes the main clinical demographics findings of these patients.

This table (Table 1) highlights that all the selected cases were pediatric, pre-lingual, and not oralized. In 50% of the cases, it was found that there were a presence of otoacoustic emissions with absence/abnormalities at ABR, and in the rest of the patients, AN was suspected and supported by the presence of CM.

Figure 1 shows the performance of patients according to the language, speech, and hearing evaluation through the application of the scales IT MAIS, MUSS, and GASP. In patients over the age of five (5) years, the GASP was used to assess the language, and in the younger ones, the MUSS was selected to evaluate this topic. IT MAIS had a focus on the largest review of the hearing improvement.

In The Glendonald Auditory Screening Procedure (GASP) analysis (p=0.002), there was a statistically significant improvement with the
The use of CI. There was better performance trend with the CI on the assessment by IT MAIS (p=0.054). Regarding the MUSS, no relevant statistical significance (p=0.35) was obtained in this topic evaluation.

Table 2 demonstrates the audiometric data of patients preoperatively, with the use of hearing aids (individual sound amplification devices), and after surgery with the use of CIs. Statistical evaluation compared the preoperative time (with the use of hearing aids) with the postoperative time (with the use of CI). There was a statistically significance at all frequencies analyzed, with p<0.05.

The patients were divided into two groups, regarding the age when they were submitted to CI surgery. Group 1 was implanted before 4-years old and Group 2 patients were implanted at more than 4-years old. Each group comprised five patients and we did not find any difference between the groups (p>0.05) in all the analyses, except that the Group 1 patients had more time using the CIs, which is normal because they were submitted to the surgery earlier than the other patients.

We also tried to perform two groups regarding the residual hearing. One group involved patients that had residual hearing (low/moderate hearing loss), while the other group had no residual hearing (severe/profound hearing loss), and we did not find any difference between the groups (p>0.05) in all the analyses.

**DISCUSSION**

The Auditory Neuropathy (AN) is a form of sensorineural hearing loss recently described and it is estimated that its prevalence is about 10-15% of newborns with sensorineural hearing loss [30].

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**Table 1. Demographic clinical data of the patients**

<table>
<thead>
<tr>
<th></th>
<th>4 years and 4 months variation: 2 years and 6 months to 6 years and 1 month</th>
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<tbody>
<tr>
<td>Age at surgery time</td>
<td>Average: 4.31 years, Median: 4.15 years, Standard deviation: 1.4726 years</td>
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<tr>
<td>CI - duration of use</td>
<td>Average: 5.24 years, Median: 2.92 years, Standard deviation: 4.5319 years</td>
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<tr>
<td>Gender</td>
<td>7 M: 3 F</td>
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<tr>
<td>OAE</td>
<td>50% presents</td>
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<tr>
<td>CM</td>
<td>50% presents</td>
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<td>ABR</td>
<td>100% absent or abnormal</td>
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<tr>
<td>Genetics findings</td>
<td>50% - mutations - homozygous at GJB2 gene (c.35delG/c.35delG), 70% - no mutations (normal)</td>
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<tr>
<td>Onset of symptoms</td>
<td>100% at congenital age</td>
</tr>
<tr>
<td>Anatomical changes (CT and MRI)</td>
<td>Normal-No abnormalities at 100% of the cases</td>
</tr>
<tr>
<td>Etiologic factors</td>
<td>Prematurity - 60% (mean 33 weeks), NICU - 60% (average 25 days), Family background - 10% brother with HNS, Neonatal jaundice - 10%, Cardiopulmonary stop- 10% (neonatal), Meningitis - 0 cases</td>
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<td>Postoperative satisfaction (VAS - visual analog scale)</td>
<td>Average: 7.7 points, Median: 8 points, Standard deviation: 1.1595 points</td>
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<td>Total</td>
<td>10 patients</td>
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CI: cochlear implant; OEA: otoacoustic emission (distortion product); ABR: auditory brain stem response; CT: computed tomography; RNM: nuclear magnetic resonance

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**Figure 1.** Performance of patients on the scales of IT MAIS, MUSS, and GASP

The use of CI. There was better performance trend with the CI on the assessment by IT MAIS (p=0.054). Regarding the MUSS, no relevant statistical significance (p=0.35) was obtained in this topic evaluation.

Table 2 demonstrates the audiometric data of patients preoperatively, with the use of hearing aids (individual sound amplification devices), and after surgery with the use of CIs. Statistical evaluation compared the preoperative time (with the use of hearing aids) with the postoperative time (with the use of CI). There was a statistically significance at all frequencies analyzed, with p<0.05.
The degree of hearing loss found in patients with AN varies from moderate to severe and the treatment of these patients is a special challenge for physicians and speech therapists, since the audiométric thresholds tend to fluctuate, as well as the measurements of speech performance. Those described situations and parameters above in many times do not correspond to the degree of hearing loss [30].

Classic and accepted CI criteria do not include AN as one of their treatment options, especially in cases where there is AN with pure tone thresholds consistent with mild to moderate hearing loss, which could be considered as a nonsense indication.

Recently, several groups of specialists in hearing surgical rehabilitation began to indicate CI to their patients with NA. Those patients were submitted to CI when they did not show improvements with the standard “medical treatment” (speech therapy and/or hearing aids). This resulted in a change of concepts and paradigms and generated further discussion among professionals involved and about the interfaces with the AN patients.

The discussions and arguments are very complex, since most patients are pediatric and naturally not oralized. This is a great difficulty because it does not allow simple and objective assessments of the indication of CIs used in oralized deaf patients (post-lingual), such as the speech perception test.

Table 2. Audiometric findings of the patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time</th>
<th>250</th>
<th>500</th>
<th>1</th>
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<th>SRT</th>
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<td>1</td>
<td>Pre-op</td>
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<td>Pre-op with HA</td>
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<td>110</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>85 dB</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-op with CI</td>
<td>55</td>
<td>50</td>
<td>45</td>
<td>50</td>
<td>50</td>
<td>40</td>
<td>50</td>
<td>85</td>
<td>70 dB</td>
<td>82%</td>
</tr>
</tbody>
</table>

frequencies in Hertz (Hz); SRT: speech recognition threshold; SRI: speech recognition index; NA: not applicable/unrealized; HA: hearing aids; CI: cochlear implant
This test (speech perception) has a fundamental importance for indicating and monitoring patients that are to be submitted to CIs, but it has extremely limited use in not oralized patients.

So, for not oralized patients, subjective rating scales are used that focus on language and hearing gains. Such scales are for the most part subjective and often the application depends on the support and active participation of parents/carriers, since these patients are children and are not oralized.

Several reports indicate that child users of CI show great variability in relation to its results. A possible cause for this variation is the impact of cognitive impairment or the present development within one-third of the patients with AN and this can affect the performance results with CI [31].

In Cameron study [31], children with the diagnosis of AN without these confounding factors and who had received CI presented language development comparable to that of other children with sensorineural hearing loss also treated with CI.

Another recent paper highlighted 17 children who had just AN, while another nine had some cognitive or associated development deficits. The two groups were compared with patients treated with CI due to sensorineural hearing loss of cochlear origin, and it was shown that children with AN without other factors and the cochlear loss group showed similar results regarding hearing with CI surgery, while nine patients with associated disease showed some benefit with CI, but this was dependent on non-aural ways of communication (signal/gesture language) [31,32].

In an Asian analysis, two patients with AN, with post-lingual/oralized hearing loss (one moderate and one severe), underwent unilateral CIs and were followed for 6 months. After 6 months of CI use, the patients showed an improvement in auditory thresholds with the use of the CI, with an average of 35 and 44 dB, respectively, and also had improved speech recognition [33].

The Glendonald Auditory Screening Procedure (GASP) rating scale shows that if the treatment is beneficial, the patient approaches an ideal result (close to 100%) in the first year of CI use. A delay of around 24 months was necessary to achieve this goal (hit rate close to 100% in GASP) in the patients studied in this study, and showed a not so great improvement in the first year of CI use.

The performance in IT MAIS was better in patients compared to the performance by MUSS; however, it needs to be pointed out that IT MAIS has a greater focus on evaluation of the hearing, while the MUSS has a greater focus on oral language.

We believe that, despite these results in these rating scales, this should not be viewed with pessimism. There are publications of patients with NA achieving good results but more slowly with good recognition and categorization of words with increased CI usage time [8, 31,32].

An important longitudinal prospective study that followed up to 140 children with AN, in which 52 (37%) of them received CIs, highlighted that AN is a very heterogeneous clinical situation with an ample diversification of impairments. However, cochlear implantation could be a very good option for helping those children to achieve great hearing rehabilitation and speech development. Poor prognosis is related to central nervous diseases and multiple deficiencies. Here electrically-evoked intracochlear compound action potential testing may be helpful to select patients with AN as potential good candidates to receive a CI [34].

It should be noted that the measure of pure tone thresholds, the recognition rate of speech, and the speech perception test are objective measures of great importance in indicating and monitoring patients with CI, particularly with oralized patients (post-lingual). But these tests have limitations, especially in not oralized patients.

This study showed improvement in all parameters of pure tone audiometry and the speech preoperative recognition index (with the use of hearing aids) and postoperative (with CIs), with a statistical significance (p<0.05).

Such data in pre-lingual and not oralized patients, usually found in children and also in cases of AN, as well as all other cases in this article, are secondary and only corroborate and support the benefits of language development of this therapeutic modality. Such benefits are valued mostly for subjective evaluations, often with the support and use of information from parents and/or caregivers and through scales that measure hearing and language improvements as used (GASP, IT MAIS, and MUSS).

Speech therapy before and after CI surgery is very important for the acquisition and development of speech. Our patients underwent this treatment in their hometown cities and there was no standardization of how this therapy occurred. With a standardized and regular speech therapy, it is possible that our results would be even more satisfying.

Cochlear Implantation is becoming a choice of treatment for patients with AN. This kind of hearing disorder with mild to moderate hearing loss is still a challenge regarding the treatments options, even to experts in this area.

This paper adds data to support CI as a treatment for AN patients and is the first Brazilian-Latin American review on this topic, and also has a greater importance for a better reflection and emplacement of clinical and management decisions. It is still necessary to study more patients and a larger study group to gain more significance data to support the conclusions of this study.

Auditory Neuropathy (AN) is a heterogeneous situation and is very difficult to study and analyze patients and outcomes. Besides, this is also a very rare condition. We did not find any difference between the groups (p>0.05) in all the analyses related to the age of implantation, except that the Group 1 patients (CI before 4-years old) had more time of use with their CIs, which is normal because they were submitted to the surgery earlier than the others patients. Regarding residual hearing (low/moderate hearing loss vs. severe/profound hearing loss), we also did not find any difference between the groups (p>0.05) in all the analyses.

The statistical significance demonstrated through the GASP analysis and audiometric findings, and the correlation trend with the IT MAIS, are the strong indicators of the benefits of using a CI in patients with AN.
The conclusion of this paper is that CI is an effective treatment for auditory rehabilitation and language development in children with AN.

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REFERENCES

1. Nikolopoulos TP. Auditory dyssynchrony or auditory neuropathy: understanding the pathophysiology and exploring methods of treatment. Int J Pediatr Otorhinolaryngol 2014; 78: 171-3. [CrossRef]


15. Santarelli R. Information from cochlear potentials and genetic mutations helps localize the lesion site in auditory neuropathy. Genome Med 2010; 2: 91. [CrossRef]


